REMARKS

Claims 1, 2, 4, 8, 9, 11 and 13-17 are pending in this application. Claim 1 is amended. No new matter is added.

In support of the remarks and arguments stated *infra*, Applicants have submitted herewith the Declaration of Dr. Howard B. Haimes.

Rejection under 35 U.S.C. §103

Claims 1, 2, 4, 7, 8, 9, 11 and 13-17 are rejected under 35 U.S.C. §103(a), as being unpatentable over U.S. Patent 5,853,703 to Cerami ("Cerami") in view of EP 0 458 589 A1 to Kabushiki ("Kabushiki"). In the Final Office Action mailed January 11, 2005, the Examiner states that while Kabushiki merely teaches a combination of prostaglandin and a cholinergic agent for lowering ocular pressure, this does not negate the fact that Kabushiki discloses known, "commercialized" cholinergic agents for treating glaucoma such as pilocarpine. Thus, since Kabushiki discloses that cholinergic agents when combined with prostaglandins are synergistically effective at lowering ocular pressure, one of ordinary skill in the art, absent evidence to the contrary, would reasonably expect cholinergic agents when combined with the thiazolium compounds of Cerami to effectively reduce ocular hypertension suffered in the patients in Cerami. *See*, Final Office Action at page 3.

In the Advisory Action mailed May 23, 2005, the Examiner indicates that the court in *In re Ball Corp.*, 18 USPQ2d 1491 (Fed. Cir. 1991) held that "obviousness does not require absolute predictability." The Examiner states that while not all of the prostaglandin compounds, when combined with pilocarpine, are effective at treating ocular pressure, Kabushiki does teach that treatment of ocular hypertension is effective, even synergistic, when certain prostaglandin compounds are combined with pilocarpine. Therefore, the Examiner submits that such a teaching is enough to raise a reasonable expectation that pilocarpine, a known anti-glaucoma compound and the claimed thiazolium compounds, when administered together, would be capable of lowering intraocular pressure. *See*, Advisory Action at page 2. Applicants respectfully disagree.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.

Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants submit that the Examiner has failed to meet the burden to establish a *prima facie* case of obviousness.

No Reasonable Expectation of Success

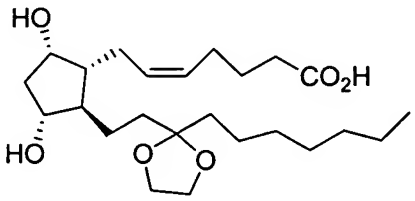
As the Examiner indicated, based on the decision of the court in *In re Ball Corp.*, it is well recognized under U.S. law that obviousness does not require absolute predictability. However, **at least some degree of predictability is required (emphasis added)**. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986). Further, it is also well recognized that a prior art reference must be considered in its entirety, *i.e.*, as a **whole**, including portions that would lead away from the claimed invention **(emphasis added)**. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983).

Applicants submit that one of ordinary skill in the art reading Cerami in combination with Kabushiki would readily recognize there is no reasonable expectation of success in combining the teachings of Cerami (thiazolium compounds) with the teachings of Kabushiki (use of prostaglandin/cholinergic agent combinations to treat ocular hypertension) to reach the present invention. Specifically, Applicants submit that the Examiner is not considering the Kabushiki reference in its entirety, as is required by *W.L. Gore & Associates, Inc. v. Garlock, Inc.* If the Kabushiki reference is considered as a whole by one of ordinary skill in the art, in combination with Cerami, it would be clear to the skilled artisan that portions of the Kabushiki reference lead away from the claimed invention. Therefore, the skilled artisan would readily recognize the unpredictability of combining distinct classes of compounds (*e.g.*, the prostaglandins taught by Kabushiki or the thiazoliums taught by Cerami) with the cholinergic agents of Kabushiki to decrease intraocular pressure or improve ocular accommodation.

Based on the Examiner's reasoning described *supra*, since both prostaglandins and cholinergic agents are art-recognized for the treatment of ocular hypertension, one of ordinary

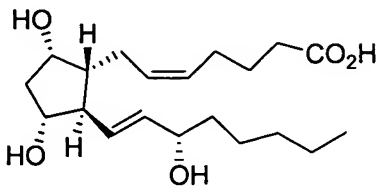
skill in the art would reasonably expect the combination of **any** cholinergic agent with **any** prostaglandin to also be able to treat ocular hypertension (**emphasis added**). This is not the case. In fact, and as stated by the Examiner, Kabushiki teaches that only **certain** prostaglandins (13,14-dihydro-15-ketoprostaglandins) in combination with cholinergic agents are able to treat ocular hypertension, albeit synergistically, while other prostaglandins ($PGF_2\alpha$) when in combination cholinergic agents **lose** their ocular pressure lowering activity (**emphasis added**). *See*, Kabushiki page 2, lines 29-30. Thus, although both classes of prostaglandins (13,14-dihydro-15-ketoprostaglandins and $PGF_2\alpha$) have very similar structures (*See*, structures comparison, *infra*) and are known in the art to treat ocular hypertension alone as a monotherapy, Kabushiki teaches that only one these classes (13,14-dihydro-15-ketoprostaglandins) is able to treat ocular hypertension when in combination with a cholinergic agent.

Compare:



13,14-dihydro-15-ketoprostaglandin

with

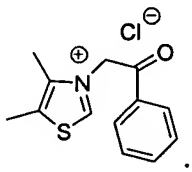


PGF2a

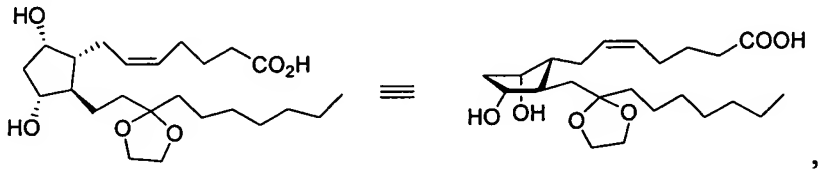
Therefore, although members of the prostaglandin family are similar in structure (all contain 20 carbon atoms, including a non-planar 5-membered aliphatic ring), their functional activity is divergent and unpredictable when combined with a cholinergic agent, such as pilocarpine. *See*, Haimes Declaration ¶ 6.

One of ordinary skill in the art reading Cerami in combination with Kabushiki, as a whole, would readily recognize there is no reasonable expectation of success in combining any prostaglandin with any cholinergic agent because the functional activity of the combination is unpredictable and obviousness requires at least some degree of predictability. The skilled artisan would further readily recognize that if there is such functional unpredictability amongst prostaglandin family members when in combination with a cholinergic agent, there is no reasonable expectation of success in combining the thiazolium compounds of Cerami with the cholinergic agents of Kabushiki to reach the present invention. *See*, Haimes Declaration ¶ 7.

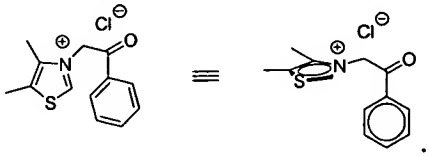
Thiazoliums are aromatic 5-membered rings, which have the special property of being flat, planar molecules. The thiazolium compounds of the instant invention are heteroaromatic, charged molecules which inhibit or reverse the formation of advanced glycosylation of proteins (advanced glycosylation end products, AGEs). One example includes 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride:



On the other hand, prostaglandins are a well known group of naturally occurring lipid molecules which are derived from fatty acids and present in virtually all tissues and organs. Prostaglandins act on a variety of cells such as vascular smooth muscle cells causing constriction or dilation, on platelets causing aggregation or disaggregation and on spinal neurons causing pain. Prostaglandins are most commonly known in the art to cause muscular constriction and mediate inflammation. Every prostaglandin contains 20 carbon atoms, including a 5-membered aliphatic carbon ring. The 5-ring structure of prostaglandins is, however, not planar. *See*, Haimes Declaration ¶ 8. For example, the prostaglandin, 13,14-dihydro-15-ketoprostaglandin, of Kabushiki is thought to have the following structure:



whereas the 5-membered ring in the thiazolium compounds of the invention (exemplified below by 3-(2-phenyl-2-oxoethyl)-4,5-dimethyl-thiazolium chloride) has a flat, planar structure:



Since prostaglandins and thiazolium compounds are structurally and functionally distinct, and because the teachings of Kabushiki, as a whole, show that the combination of any prostaglandins with any cholinergic agents is not reasonably expected to be effective in treating ocular hypertension, Applicants submit that the skilled artisan would have no reasonable expectation of success combining the methods of using the thiazolium compounds of Cerami

with the cholinergic compounds used in the methods of Kabushiki to reach the present invention. *See*, Haimes Declaration ¶ 9.

No Suggestion or Motivation

Applicants submit that one of ordinary skill in the art would not be motivated to combine the teachings of Cerami and Kabushiki to reach the present invention.

As stated by the Examiner, while Cerami discloses thiazolium compounds of Formula I and various therapeutic uses for these compounds, Cerami does not teach or suggest methods of decreasing intraocular pressure or improving ocular accommodation by administering the compounds of Formula I. However, the Examiner asserts that although Cerami does not explicitly teach decreasing intraocular pressure or improving ocular accommodation, this would have been inherent in the disclosed method which discloses administration of identical active agents in identical dosages to a host in need thereof, using Applicants' claimed method steps. *See*, June 17, 2004 Office Action at pages 4-5. Applicants traverse.

Applicants submit that Cerami does not teach or suggest methods of decreasing intraocular pressure or improving ocular accommodation by administering the compounds of Formula I explicitly or inherently. Specifically, the patient population disclosed in the present specification is not taught or suggested, explicitly or inherently, by the patient population disclosed in Cerami.

It is well established that "in relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic **necessarily** flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461 (Bd. Pat. App. & Inter. 1990) (**emphasis in original**).

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 49 USPQ2d 1949 (Fed. Cir. 1999). In order to find inherent anticipation, the undisclosed element of the prior art had to be a necessary technological fact of the prior art. *Continental Can Co. v. Monsanto Co.* 948 F.2d 1264, 20 U.S.P.Q.2d (BNA) 1746 (Fed. Cir. 1991). It is inadequate to show that the prior art process would probably, or possibly, produce the undisclosed element. *Id.* Rather, the

undisclosed element had to flow as a natural consequence from the technological constraints of the prior art. *Id.*

Therefore, the fact that a certain result or characteristic **may** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993) **(emphasis in original)**.

The present specification discloses methods of treating or ameliorating glaucoma, decreasing intraocular pressure and increasing ocular accommodation by administering the thiazole, imidazole and oxazole compounds of Formula I to subjects in need thereof. Cerami merely discloses methods of treating or ameliorating diabetes, diabetic retinopathy or cataracts by administering the disclosed thiazole compounds I to subjects in need thereof. Cerami does not disclose glaucoma, intraocular pressure or ocular accommodation. Thus to establish that Cerami inherently anticipates the present claims, the Examiner must establish that the undisclosed element of the prior art (*i.e.*, glaucoma, intraocular pressure or ocular accommodation) must necessarily flow as a natural consequence from the disclosure of Cerami. Applicants respectfully submit that the Examiner has failed to meet this threshold.

One of ordinary skill in the art would readily recognize that the etiology, symptoms and treatment of glaucoma/increased intraocular pressure is quite different from that of diabetic retinopathy or cataracts.

The eye constantly produces aqueous humor, the clear fluid that fills the anterior chamber (the space between the cornea and iris). The aqueous humor filters out of the anterior chamber through a complex drainage system. The delicate balance between the production and drainage of aqueous humor determines the intraocular pressure. Normal human intraocular pressure ranges between 8mm and 21mm Hg. Increased intraocular pressure indicates a problem with the amount of aqueous humor in the eye: either the eye is producing too much, or it's not draining properly. High intraocular pressure is a major risk factor for glaucoma. Glaucoma is an eye disorder that causes progressive and irreversible optic nerve damage and vision loss.

Although not everyone with intraocular pressure above 20mm Hg develops glaucoma, someone with the pressure over 20mm Hg is more likely to develop glaucoma than someone with a lower pressure. Also, there are some people who have an intraocular pressure below 20mm Hg who develop glaucoma, this is called normal tension glaucoma.

Depending on the type of glaucoma, various symptoms may be experienced. There is gradual loss of peripheral vision and night vision. Blurred vision and colored rings around lights accompany these symptoms. If intraocular pressure remains high, tunnel vision can develop.

Glaucoma Risk factors include age, race (African-Americans and persons of Japanese decent have a higher incidence of glaucoma), sex (females are high risk), family history and medical disorders (*e.g.*, presence of hyperopia or farsightedness, diabetes or previous eye injury). Although glaucoma cannot be cured, in most cases it can be successfully controlled. Glaucoma treatment entails decreasing aqueous humor production, increasing fluid drainage or a combination of the two, thereby decreasing intraocular pressure. Intraocular pressure treatment may be in the form of medication (*e.g.*, eye drops containing beta-blockers or alpha-2 agonists), laser therapy or surgery (*e.g.*, trabeculoplasty, trabeculectomy). *See*, Haimes Declaration ¶ 10.

Diabetic retinopathy is a disorder of the retinal blood vessels resulting from diabetes. Everyone who has diabetes is at risk for developing diabetic retinopathy, but not all diabetics do develop it. The incidence of diabetic retinopathy increases with the duration of diabetes. About 60% of patients having diabetes for 15 years or more will have some blood vessel damage in their eyes and a percentage of these are at risk of developing blindness. Patients with diabetic retinopathy are also at a greater risk of developing retinal tears and detachment.

In diabetic retinopathy, the small blood vessels that are in the retina are damaged and become leaky. New blood vessels can also grow in the back of the eye. These new vessels are abnormal and bleed easily, sometimes filing the back of the eye with blood. This causes the retina to swell and form deposits. The affect of diabetic retinopathy on vision varies widely, depending on the stage of the disease. Some common symptoms include blurred vision, floaters and flashes and sudden vision loss. Risk factors for diabetic retinopathy include high blood glucose, poor diet and lack of exercise.

Diabetic retinopathy is treated in many ways, depending on the stage of the disease and the specific problem that requires attention. The preferred method of treatment is laser photocoagulation to seal off leaking blood vessels and destroy new growth or in more extensive cases, vitrectomy. Many patients control their diabetes with diet and medication to delay or prevent the development of diabetic retinopathy and other complications.

Although diabetes and diabetic retinopathy are risk factors for increased intraocular pressure and glaucoma, not all diabetics or people suffering from diabetic retinopathy develop increased intraocular pressure or glaucoma. In fact, while most diabetics develop diabetic

retinopathy over time, the same cannot be said for intraocular pressure and/or glaucoma. Specifically, the instant specification teaches that primary open angle glaucoma (the predominant form of glaucoma) occurs in approximately 4% of diabetics compared to 1.8% of the general population. *See*, page 1, lines 18-32. *See*, Haimes Declaration ¶ 11.

Cataracts are a disorder characterized by a clouding of the eye's natural lens, which lies behind the iris and the pupil. The lens is mostly made of water and protein. The protein is arranged in a precise way that keeps the lens clear and lets light pass through it. But as people age, some of the protein may clump together and start to cloud a small area of the lens. This is a cataract, and over time, it may grow larger and cloud more of the lens, making it harder to see. Cataracts are classified as one of three types: nuclear, cortical or subcapsular. The type of cataract you have will affect exactly which symptoms you experience and how soon they will occur.

In general, it is not clear why the eye's lens changes over time, forming cataracts; however, risk factors include exposure to ultraviolet light or other forms of radiation, cigarette smoke, air pollution, heavy alcohol consumption, diet high in salt, diabetes and the use of steroids, diuretics and major tranquilizers

When symptoms begin to appear, vision may be improved temporarily using new glasses, strong bifocals, magnification, appropriate lighting or other visual aids. However, cataract surgery, which involves the replacement of the clouded lens with a clear, plastic intraocular lens, is recommended for most cataract sufferers and is very successful in restoring vision.

Cataracts are a separate disorder, unrelated to glaucoma or increase intraocular pressure. The only relation between cataracts and glaucoma or increase intraocular pressure is that these disorders share diabetes as one risk factor. *See*, Haimes Declaration ¶ 12.

Applicants submit that to establish inherency, it is inadequate to show that a diabetic or subject suffering from diabetic retinopathy or cataracts would probably, or possibly, develop glaucoma or intraocular pressure despite the fact that diabetes is a risk factor for developing glaucoma or increased intraocular pressure. One of ordinary skill in the art would readily recognize that while diabetics are twice as likely to develop glaucoma or increased intraocular pressure as compared to the general population, glaucoma and increased intraocular pressure are not a **natural** consequence that necessarily flows from diabetes, diabetic retinopathy or cataracts (**emphasis added**). *See*, Haimes Declaration ¶ 13.

For the foregoing reasons, Applicants submit that Cerami does not teach or suggest, explicitly or inherently, methods of decreasing intraocular pressure or improving ocular accommodation by administering the compounds of Formula I.

Applicants submit that Kabushiki does not cure these deficiencies of Cerami. Kabushiki merely discloses the combination of a cholinergic agent and a specific prostaglandin compound (13,14-dihydro-15-ketoprostaglandin) to treat ocular hypertension. Kabushiki does not teach or suggest thiazolium compounds. Further, one of ordinary skill in the art would readily recognize that the thiazolium compounds of the instant invention and prostaglandins are structurally distinct and possess very different biological activities.

Applicants submit that based on the structural and biological differences between the thiazolium compounds Cerami and the prostaglandin family, described in detail above, one of ordinary skill in the art would not be motivated to combine Cerami and Kabushiki. The fact that references can be combined or modified does not render the resulting combination obvious unless the prior art also suggests the desirability of the combination. (*See* MPEP §2143.01, citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)). As described above, there is no suggestion in either reference that would motivate a skilled artisan to modify the methods to decrease intraocular pressure using a combination of a thiazolium compound of formula I and a cholinergic agent. Thus, the mere fact that the Cerami and Kabushiki references can be combined is not sufficient to establish a *prima facie* case of obviousness.

Applicants respectfully request this rejection should be withdrawn.

CONCLUSION

On the basis of the foregoing amendment and remarks, Applicants respectfully submit that the pending claims are in condition for allowance and a Notice of Allowance for the pending claims is respectfully requested. If there are any questions regarding this application that can be handled in a phone conference with Applicants' Attorneys, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Ivor R. Elrifi, Reg. No. 39,529
Matthew Pavao, Reg. No. 50,572
Attorney/Agent for Applicant
c/o MINTZ, LEVIN
Tel: (617) 542-6000
Fax: (617) 542-2241
Customer No.: 30623

Dated: October 12, 2005